

Are the Infectious Roots of Alzheimer's Buried Deep in the Past?

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Abstract

Recent literature shows a controversial new push to tie microorganisms to Alzheimer's disease (AD). Study after study, in which scientists have injected human Alzheimer-diseased brain tissue into mice and other laboratory animals that later developed the disease have left little doubt that Alzheimer's disease (AD) arises from an infectious process. By 2013 Mawanda and Wallace's "Can Infections Cause Alzheimer's Disease" struck down some of the commonly entertained pathogens for AD such as herpes simplex virus type 1, Chlamydia pneumoniae, and several types of spirochetes. Instead they pointed to two prime suspects for Alzheimer's amyloid-beta deposition: "especially chronic infections like tuberculosis and leprosy." To be sure, it was German neuropathologist Oskar Fischer of the Prague school of Neuropathology, Alzheimer's great rival, who was the first to suggest that infection might be causative for Alzheimer's. Fischer's credentials: he was the co-discoverer of Alzheimer's disease. His suspected germ was the Streptothrix, today classified as Actinomycetes, a rare central nervous system pathogen which at the time was so constantly and consistently mistaken for tuberculosis that Choppen-Jones suggested that TB be called tuberculomycosis. And Just ten years before Oskar Fischer found Actinomycosis-like forms in Alzheimer's cerebral plaque, Babès and immunologist Levaditi reported in "On the Actinomycotic Shape of the Tuberculous Bacilli" that Fischer's typical Actinomyces-like clusters (Drüsen) with clubs appeared in the tissue of rabbits inoculated with tubercle bacilli beneath the dura mater of their brains. Investigators who supported and subsequently followed up on Fischer's Alzheimer's germ are also discussed.

Keywords: Alzheimer's disease; Infectious Cause of Alzheimer's Disease; Oskar Fischer; Alois Alzheimer; Neurodegenerative Disease; Neurotuberculosis

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Introduction

By February 9th, 2016 the Journal of Alzheimer's disease (JAD) accepted an informative Editorial entitled "Microbes and Alzheimer's Disease" by Neurobiologist Ruth Itzhaki and others, signed-off on by 31 scientists from around the world [1]. Much of that Editorial rehashed subject matter already addressed by Mawanda and Wallace in "Can Infections Cause Alzheimer's Disease", just three years (2013) before [2].

Itzhaki also appeared in a 1997 piece for Lancet, regarding Herpes simplex virus type 1 in conjunction with APOE-epsilon 4 allele as a strong risk factor for AD, though either of these features alone, she mentioned up front, do not increase the risk of AD [3]. People who have symptoms of late onset Alzheimer disease (AD) and

have one or more APOE e4 copies are more likely to have AD. However, this is not diagnostic of AD, nor should it be used to screen asymptomatic people or their family members. Many of those who have e4 alleles will never develop AD. And even in symptomatic people, only about 60% of those with late onset AD will have APOE e4 alleles [4,5].

The topic of Alzheimer's as of infectious disease origins has been accepted by many, but some of the specific infectious agents mentioned by Itzhaki et al. as possibly being responsible for Alzheimer's disease are open to question. Specifically, Itzhaki has implicated the following agents found in the elderly brain as possibly causative to Alzheimer's: (1) herpes simplex virus type 1 (HSV-1), (2) Chlamydia pneumoniae, and (3) several types of spirochetes. Also mentioned were (4) fungal infection in the AD

brain as well as (5) abnormal microbiota (commensal, symbiotic and pathogenic microorganisms that literally share our body space) which have already been found in the blood of Alzheimer's patients [1].

On the other hand, Mawanda and Wallace's review (2013) had already given seven annotated references as to why HSV-1 "remains questionable" as a cause for Alzheimer's; nine studies referencing as to why there was "no evidence to suggest an association between Chlamydia pneumoniae infection and AD pathogenesis"; and six "rigorous studies which found no evidence to suggest that spirochetal *B. burgdorferi*, is "causally linked to AD." [2] Wallace also mentioned that although Riviere et al. found oral spirochetal *Treponema*, including *T. denticola*, *T. pectinovorum*, *T. vincentii*, *T. amylovorum*, *T. maltophilum*, *T. medium*, and *T. socranskii* in a significantly higher proportion of postmortem brain specimens from AD cases than controls, [6] that these results have, however, not been replicated. Furthermore, Oskar Fischer, the discoverer of Alzheimer's plaque, failed to observe it in the brains of 45 cases with neurosyphilis [7]. In fact even Alzheimer himself and E.E. Southard of Harvard, both experts on the detection of neurosyphilis –never implied that syphilis was even nearly behind the bulk of Alzheimer's cases. And while one out of the four cases that Alzheimer turned over to his colleague Perusini had neurosyphilis, that case also had a lung scarred by a previous encounter with tuberculosis.

What Mawanda and Wallace did maintain, however, was the emerging evidence that supported an infectious pathogen and two prime suspects for Amyloid beta deposition to the extent that it was going on in Alzheimer's. They said this:

"In addition, amyloidopathy—a condition characterized by elevated levels of serum amyloid and by amyloid deposition and aggregation in tissues—is a frequent occurrence in several acute and chronic systemic inflammatory conditions, especially chronic infections like tuberculosis and leprosy." IBID(2) p.162

And there seemed to be no dearth of studies referenced to substantiate that statement [8-14].

As for Alois Alzheimer himself, he was already too bogged down by his boss Emil Kraepelin's edict that Alzheimer's disease be a new disease to get involved in specifically what caused it. So instead Alzheimer would continue to speak about and probe the gross pathology of what he had found in Alzheimer's disease:

"Very remarkable and really without precedent in the pathological anatomy of the nervous system are the alterations of (brain neuron) axis-cylinders (the central core of the axon of in this case brain neurons), so exhaustively described by Fischer." [15]

But, in reality nothing Alzheimer mentioned was without "precedent." True, Fischer, Alzheimer's great European rival, was credited with establishing senile dementia, which Fischer felt was part and parcel of Alzheimer's disease –and he exhaustively worked on the alterations to axon cores in Alzheimer's. Yet Barlow, [16] in describing neurotuberculosis seven years prior to Alzheimer and Fischer's work, mentioned both Fischer's degenerative plaque alterations in the brain's neuronal axis-

cylinders and Alzheimer's own observation with regard to the fibrillary degenerative tangles of cerebral ganglion cells under tuberculous attack. Here is Barlow's explanation for such tubercular "plaques" and "tangles":

Microscopic investigations throws some light upon this condition (cerebral tuberculosis): The deposition of miliary tubercle in the subarachnoid, and along the ingrowing processes of pia mater, not only interferes with the vascular nutrition of the brain substance, but actually invades it, giving rise to extensive cellular infiltration, and causing degeneration of both axis-cylinders (of brain neurons) and ganglion cells. This seems to justify the modern designation of the disease as a true (tubercular) meningoencephalitis [16].

Also, it is improbable that Alois Alzheimer did not read and absorb the parallels between Otto Ranke's work on central nervous system tuberculosis and his own histological findings on Auguste Deter's brain [17]. Alzheimer and his lifetime friend, Franz Nissl, began to jointly edit the journal *Histologische und histopathologische Arbeiten über die Grosshirnrinde*—a publication Ranke's TB meningitis review was accepted into and then published in 1908.

Despite such knowledge of possible linkage between cerebral tuberculosis and Alzheimer's disease—an association implied not only by Alzheimer's German and European colleagues but subsequently by Southard at Harvard and Clouston at Edinburgh –and despite the seven million deaths per year from a tubercular disease that led to TB sanatoria sprouting up like weeds all around him—Alzheimer's silence was singular (**Figures 1 and 2**). Alzheimer doubled down on his carefully manicured hypothesis, repeatedly beseeching neurologists and psychiatrists alike not to look toward "well-known disease" as being behind this "new disease." After all, it had to be a "new" disease because Alzheimer's chief, Emil Kraepelin, demanded that it be new.

Department of Neuropsychiatry, the German University of Prague, Prague, Czechoslovakia, 1907

It thus becomes a matter of great curiosity and interest that from the beginning, Alois Alzheimer's main rival, German neuropathologist Oskar Fischer, thought he had spotted, throughout his Alzheimer's brain autopsies, a tubercular-like germ called *Streptothrix*, often confused with the filamentous forms of the tubercular bacilli (**Figure 3**). For Fischer, this was the possible infectious cause of Alzheimer's.

Fischer's findings were never meant to be taken lightly. Historical circumstance mandates that we owe as much to Oskar Fischer for the discovery of Alzheimer's disease as to Alois Alzheimer himself. Doubters have to go no further than Alzheimer's 1911 paper, which is in part a running dialogue between Alzheimer's own feelings and findings and those of the Prague Institute of Neurology's Dr. Oskar Fischer [18]. Indeed, the only reason why what we call "Alzheimer's disease today is not called "Alzheimer-Fischer's disease" or just "Fischer's disease" has simply to do



Figure 1 Some of the other fortress-like TB sanatoria dotting Germany circa Alzheimer’s time. (From F. R. Walters, Sanatoria for Consumptives, Swan Sonnenschein & Company, Ltd., London, 1899).

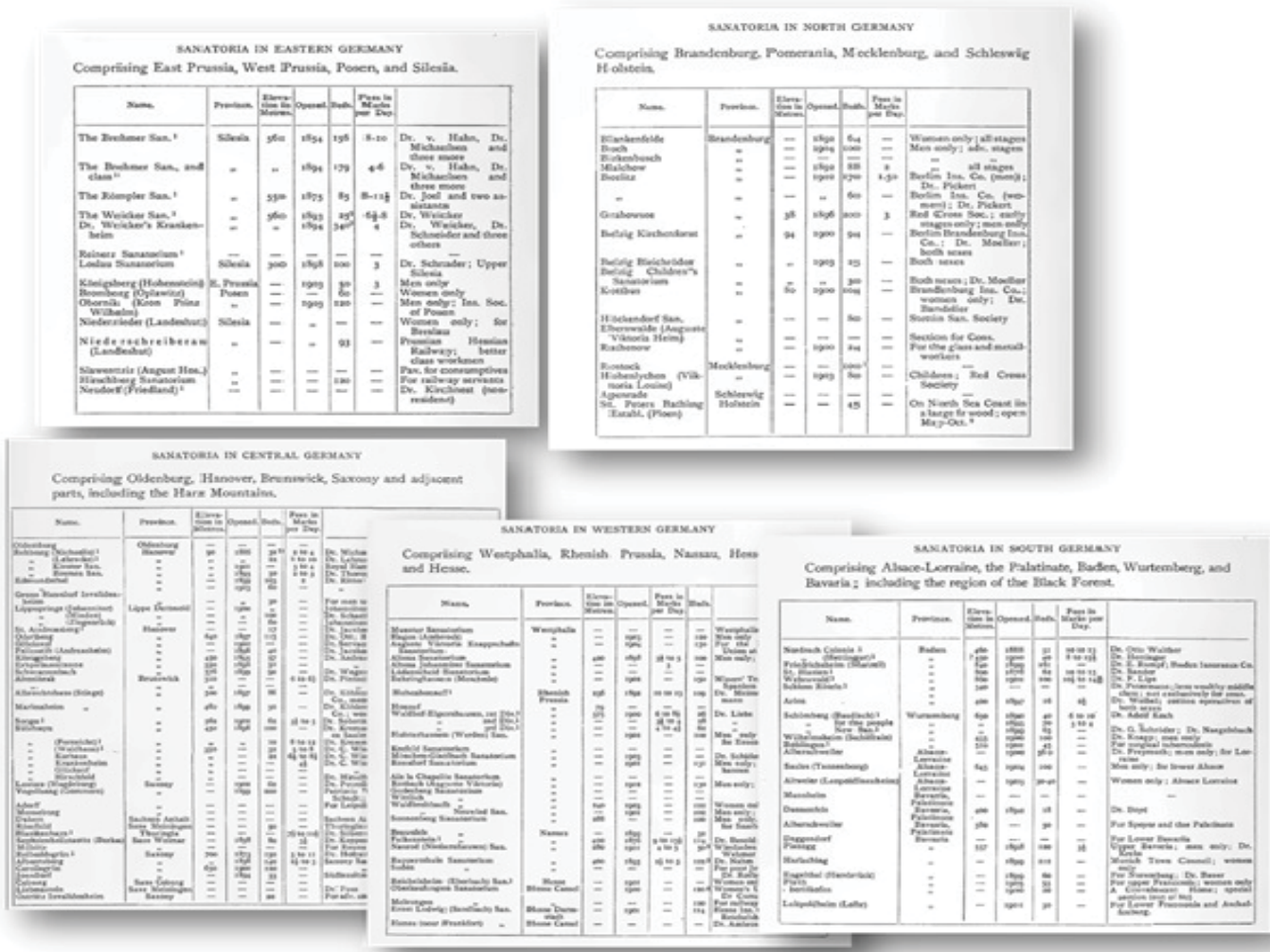


Figure 2 A more comprehensive list of the burgeoning, ever-growing German TB treatment sanatoria operative throughout unified Germany during Dr. Alzheimer's career (From F. R. Walters, Sanatoria for Consumptives, Swan Sonnenschein & Company, Ltd., London, 1899).



Figure 3 Alzheimer's great rival, Oskar Fischer (1876–1942), around the time of his sixtieth birthday in 1936.

with the course of world history, the rise of Nazi Germany, and Alzheimer's boss, Emil Kraepelin, high priest of early German psychiatry.

A Prague neuropathologist of German-Jewish origin, for years Oskar Fischer's presbyophrenia –a form of senile dementia characterized by marked memory loss - and Alzheimer's disease, supposedly a "presenile" dementia, were used interchangeably. And in a 1916 review, Spielmeyer, who would eventually replace Alzheimer at Munich, revealed that even Alzheimer himself knew that the presenile decline he had "discovered" in people in their late forties, fifties, and early sixties was nothing really new [19]. It was simply what Fischer had already characterized with somewhat of an earlier age of onset, at a time when certain pathologic findings were more prominent.

It has also become more and more obvious that just as Oskar Fischer implicated to begin with, there is an association between dementias such as Alzheimer's and infectious disease [20,21]. Often, Alzheimer's plaque looks like colonies of bacteria, which would account for the disease's chronic inflammation that

damages brain neurons. But what has recently brought this microbial hypothesis into sharper focus than ever have been microscopic findings that microbes such as tuberculosis, a disease historically associated with human amyloidosis to begin with, can produce amyloid fibrils identical to those found in Alzheimer's plaque [22]. Moreover, such bacteria-manufactured amyloid fibrils elicit the same response from the brain's immune cells as does Alzheimer's amyloid plaque, the sticky buildup of proteins that accumulates outside of Alzheimer's nerve cells [23]. Kidd confirmed as early as 1963 that the amyloid of Alzheimer's was indistinguishable from amyloid generated by an infection such as TB [24].

But to be sure, Oskar Fischer was the first on record to suggest that infection might be causative for either Alzheimer's presenile dementia or his own senile dementia [25]. Fischer's infectious view never gained immediate popularity, although today, more than a century later, a volume of data supporting such an approach has begun to accumulate. But was Fischer's specific microbe on the right track to discovering the cause of Alzheimer's to begin with? Documents uncovered since then seem to suggest that he was considerably closer than anyone else—either then or since.

As a member of the *Prague School of Neuropathology*, headed by famed neuropathologist Arnold Pick, Oskar Fischer's credentials were flawless. At the time, the Prague school was one of two neuropathological schools in Europe. The other was in Munich, headed by Emil Kraepelin, where Alzheimer worked. Fischer's detailed drawings showed neuritic Alzheimer brain plaque with abnormal, club-shaped neurons (**Figure 4**) and small branching complexes leading to the displacement of the rest of the normal-looking nerve fibrils in the space occupied by the plaques. These were the "drüsen," occasionally club-shaped, that Fischer repeatedly wrote about.

At the time, it was widely acknowledged that such drüsen could result from either infection with *Streptothrix*, now known as *Actinomyces* (*aktinomycesdruse*), a rare disease in humans, or tuberculosis, a disease that by 1882, as Alzheimer prepared to leave for Berlin for his medical education, was understood to be far and away the leading cause of infectious death in Europe. During Alzheimer's and Fischer's lifetimes, tuberculosis's annual death rate of seven million persons per year was more than twice the approximately two to three million people some estimate it still kills annually [22]. Furthermore, clinically there has always been a subset in adults with cerebral tuberculosis whose clinical features included a slowly progressive dementia over months or years characterized by, among other things, memory deficits [26].

Tubercular cerebral plaque, one subset of which is called *tuberculoma en plaque*, was first described by French authors, notably Chantemesse in 1884, eight years before Blocq and Marinescu stumbled across their "senile" plaque [27].

Chantemesse's cerebral plaque was a chronic, proliferating, fibroid type of tuberculosis, with extensive areas involving the meninges of the brain's cortex. The average survival with such tubercular plaque-ridden brain disease was approximately seven

years. Most people who have Alzheimer's disease die within eight years of their diagnosis—typically from infection or "pneumonia," not cognitive failure.

Victor Babes might have been among the first bacteriologists, but he also had a sharp interest in the nervous system. Later he, Blocq, and Marinescu would publish *An Atlas of the Pathologic Histology of the Nervous System* [28]. Neither Blocq, Marinescu, nor Oskar Fischer were bacteriologists, but Victor Babes was. Born in Vienna, Babes at one point worked with Robert Koch in Berlin but split with him over Koch's insistence that the only form real tuberculosis could take was its bacillary form. Babes, who also worked with Pasteur, knew better (**Figure 5**).

Yet subsequently, bacteriologists Vera and Rettger of Yale openly contradicted Koch [29]. Vera wrote, "*The single point on which all investigators have agreed is that the Koch (tubercular) bacillus*



Figure 4 The thick, black, club-shaped "Drüsen" in Oskar Fischer's 1907 drawing of senile plaque. [From Fischer O. Miliare Nekrosen Mit Drusigen Wucherungen der Neurofibrillen, eine Regelmässige Veränderung der Hirnrinde bei Seniler Demenz [Miliary Necrosis with Nodular Proliferation of the Neurofibrils: A Common Change of the Cerebral Cortex in Senile Dementia]. *Monatsschr f Psychiat Neurol* 1907; 22: 361-372.]



Figure 5 Physician and early bacteriologist Victor Babes (1854–1926).

does not always manifest itself in the classical rod shape. While at times and most commonly the organism appears as a granular rod, coccoid bodies, filaments, and clubs are not rare [29]."

And so, just ten years before Oskar Fischer found Actinomycosis-like forms in Alzheimer's cerebral plaque, Babès and immunologist Levaditi reported in "On the Actinomycotic Shape of the *Tuberculous Bacilli*" that typical Actinomyces-like clusters (Drüsen) with clubs appeared in the tissue of rabbits inoculated with tubercle bacilli beneath the dura mater of their brains [30]. Once introduced into the brain this way, reported Babes, TB bacilli not only branched out like the Actinomycosis such as Streptothrix, but they developed rosettes that were identical to the "drüsen" that Oskar Fischer spotted in Alzheimer's plaque.

Neurology Clinic, Salpêtrière Hospital, Paris, France, 1892

After Gheorghe Marinescu had worked for eminent bacteriologist Victor Babès for several years, Babes arranged a valuable government scholarship that enabled Marinescu to study under Jean-Martin Charcot in Paris. There, Marinescu met Paul Blocq.

By 1892, Blocq and Marinescu described, for the first time, senile plaques as perhaps microglial nodules in the cerebral gray matter of nine deceased epileptic patients with histories of seizures [31]. Blocq and Marinescu did not relate such plaque to dementia, as Oskar Fischer did. Nor did Blocq and Marinescu stipulate what specifically might have caused such plaque, other than possibly brain microglia.

Nevertheless, Blocq and Marinescu were first to describe, upon histological examination of epileptic brains, such "small nodules" that were later named "senile plaque." Marinescu describes what he found:

"Scattered throughout the various layers of the (brain's) cortex, small round clusters with a diameter of about 60µm, distinguished from the rest of the tissue by a much more intense staining, and regular contours. They thus appear as vaguely dotted structures sprinkling the background of the slices. This is why it is possible to consider some of them at least as true multiple glial nodules. (?)"[31].

Microglia or "glia" are valuable elements in the brain's immune system. The fact is that the central nervous system (CNS) can be invaded and damaged by a variety of microorganisms. Indeed, the body's defense against such infections involves resident cells of the CNS, particularly microglia. However, it is only when microglia are activated by infection or inflammation that they produce "factors" that are detrimental and destructive to brain neurons in a culture, creating, among other things, cerebral plaque [32]. Microglia therefore are not in themselves the underlying cause of Alzheimer's plaque. More probably, an infection capable of entering them intracellularly and altering their architecture and metabolism is.

A distinctive characteristic of infection with *M. tuberculosis*, a disease that according to WHO (the World Health Organization) affects a third of the world, is its capacity to enter and replicate

within macrophages in the blood. Within the brain, microglial cells are the resident macrophages. As such, human microglial cells are productively infected with *M. tuberculosis* and are, in fact, its principal target in the CNS **Figure 6** [33-35].

And just as the microglia are TB's principal target in the brain, microglia themselves are central to the brain's response to fight cerebral TB [36]. Once infected, microglia can then serve as a reservoir of tuberculosis, surviving and possibly creating a pool or source of infection for further tubercular attack in the brain. For all of these reasons, microglia have emerged as being key to understanding the neuropathogenesis of tuberculosis in the CNS. When TB attacks and infects the microglia in the brain, unlike most pathogens, it at first resides quite comfortably in the microglia's cytoplasm within round, fluid-filled vacuoles, surviving and multiplying. Thus, TB and fowl-TB (avian tuberculosis) create their own cerebral infectious reservoirs. A short time later in such tubercular infection of the microglia, there is a retraction of the microglial processes. Tuberculosis will now direct a frontal offensive toward the brain's immune system, its virulent strains looking to inhibit the very defensive microglial cytokines that are so deadly to most other microbes [37].

By 1910, Fischer, using staining techniques more advanced than either Redlich's or Blocq and Marinescu's, was able to demonstrate that senile plaques were not proliferating glial cells but rather a particular type of deposit of independent nature that subsequently "has been shown to have an outer area of degenerated neurons, a middle zone of swollen axons and dendrites, and a central amyloid core." [38]

Blocq and Marinescu might never have connected the dots regarding why microglia might spawn senile plaque beyond their changed microglial architecture. But Marinescu's haunting drawing, detailing the anatomical study of senile plaque, uncannily resembles the microbial attack (with drüsen) laid out for Alzheimer's by Oskar Fischer **Figure 7** [39].

Nervenlinik, Department of Clinical Psychiatry, University of Munich, Munich, Germany, 1907

In the form of Oskar Fischer, Alois Alzheimer and Emil Kraepelin soon realized that they had a huge problem **Figure 8**. Alzheimer acknowledged the importance of Fischer's plaques in Alzheimer's disease. Nevertheless, Alzheimer had to try to make his case that his findings were somehow different from Fischer's. And to do so unfortunately would, in part, require raising some doubt regarding Fischer's thoughts and findings. Thus, by 1911 Alzheimer wrote the following:

"Hitherto opinions about the nature of the plaques have been very divergent. Fischer pointed out their similarity to bacterial colonies and reported that he had undertaken cultivation experiments and complement-fixation tests which however produced negative results" [18].

At the time Fischer undertook cultivation and complement fixation tests to validate his germ, negative results were the rule, not the exception. Alzheimer should have known this. Thus, the fact that

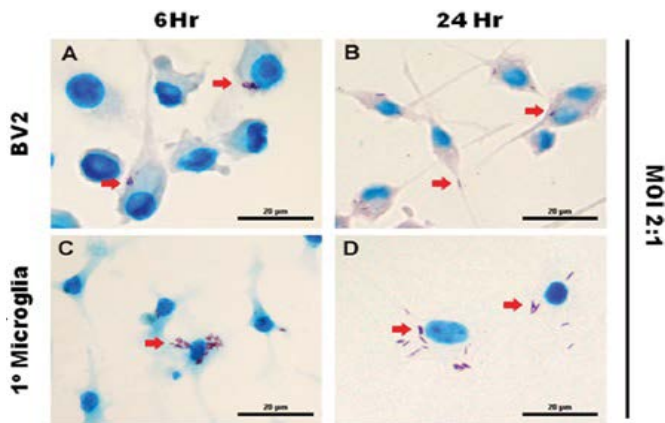


Figure 6 *M. tuberculosis* infects microglia. The microglial cell line BV2 (A and B) and primary microglia (C and D), isolated from human brain cortex infected with *M. tuberculosis* at an MOI of 2:1 for 6 and 24 h. The arrows indicate the uptake of acid-fast bacilli by the microglial cells. Scale bars, 20 μ m. Note in D the retraction of microglial processes after being infected with TB for 24 hours. [From Randall PJ, Hsu NJ, Lang D, Cooper S, Sebesho B, Allie N et al. Neurons are host cells for *Mycobacterium tuberculosis*. *Infect Immun*. 2014 May; 82(5):1880-90] with permission.

attempts at running complement–fixation tests in all cases using the serum of patients with known *Streptothrix* (Actinomycosis) patients [40]. Before that, Woodhead, Director of Laboratories at the Royal College of Physicians, pointed out that any attempted failure to cultivate *Streptothrix* could easily occur when trying to cultivate the well–developed club–shaped form of the organism that Fischer repeatedly documented. Woodhead:

“The first attempt that was at all successful was made by Bostrom, who, throwing aside the club-like processes, took for his inoculating material the central network, selecting as far as possible young growing colonies for his seed material [41].”

But even Bostrom succeeded in getting only eleven positive growths out of several hundred planted [42]. Bolton later pointed out that unlike TB, Fischer’s *Streptothrix* rarely involved the central nervous system [43]. Furthermore, although the first case of *Streptothrix* involving the CNS was reported by Ponfick [44], Harz never succeeded in cultivating the organism from there [45]. Most of this literature was readily available to the Alzheimer group.

Moreover, even in the case of using complement–fixation tests to detect the far, far more prevalent tuberculosis, Corper reported as late as 1916 that such tests were positive in only 30 percent of already–proven cases of tuberculosis– whether active or inactive [46].

Be that as it may, on November 3, 1906, Alois Alzheimer traveled to the auditorium of the Clinic for Psychiatry at the University of Tübingen, Germany, to present and describe the pathological characteristics of his “unusual” case of dementia. Alzheimer’s deceased patient, Auguste Deter, would soon become known as the first documented case of Alzheimer’s disease (AD) but not right away. At this presentation, Alzheimer also described other aspects of Deter’s autopsy, specifically the staining of abnormal neurons in her brain:



Figure 7 One of Marinescu’s drawings from his *Anatomical and Clinical Study of the So-Called Senile Plaques*, Marinescu G. (1912), *Encephale* (Paris), 1er semestre, pp. 105:32. This drawing depicts senile plaque using silver stain with an outer layer of fibers that are short and thick with other thinner fibers present. Some are almost club-shaped, as in the drüsen of Oskar Fischer.

Fischer’s cultivation experiments and complement fixations were negative did not rule out the existence of Fischer’s brain microbe.

For example, in the same year that Alzheimer made his 1911 statement, Harbitz and Grondahl reported repeatedly negative

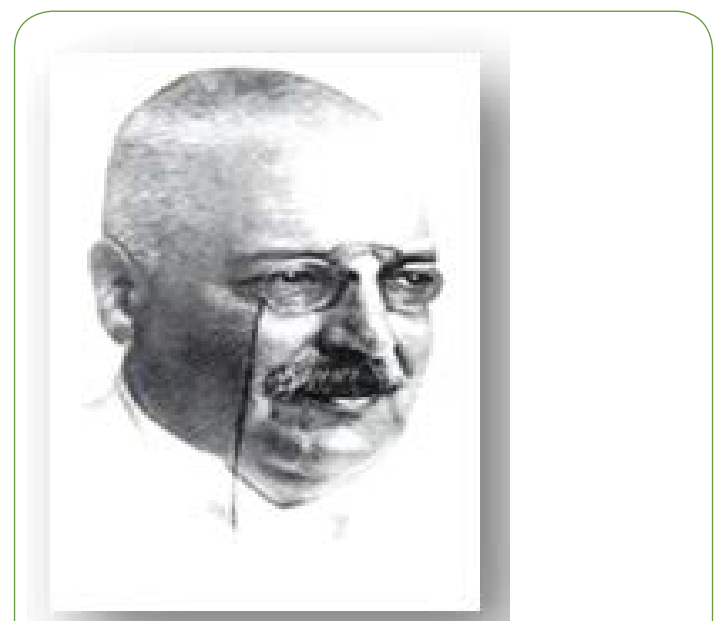


Figure 8 Alois Alzheimer (1864–1915) became research assistant to Emil Kraepelin at the Munich medical school in 1903.

“Because these fibrils were stained differently from normal neurofibrils, a chemical conversion of the neurofibrils must have occurred. This may well explain why the fibrils survived the decay of cells” [47].

Yes, a chemical conversion. But from what? First there were technical considerations concerning the stain used. Key to Alzheimer and Oskar Fischer being able to find Alzheimer’s pathology was their use of the reduced silver staining technique developed by Max Bielschowsky [48,49]. Bielschowsky’s stain impregnated silver into nerve fibers using chemicals shared by photographers. Bielschowsky believed he had come across a fairly reliable way to stain what he was already referring to as abnormal “neurofibrils”. Indeed, when both Alzheimer and Fischer used the stain, they noticed increased staining in many of the brain’s pathological cortical nerve cells. Alzheimer’s assistant, Gaetano Perusini, praised Bielschowsky’s method, observing that “by this method the plaques are seen impregnated more or less intensely with silver nitrate” [50]. By 1911, however, Bielschowsky also knew that his stain impregnated more than just neurofibrils—findings which drew surprisingly little attention from early Alzheimer’s investigators. Many structures, including portions of the cerebral blood vessels, under pathologic conditions, could stain with his stain. Also Bielschowsky reminded his colleagues that when lipid accumulated in diseased nerve cells, neurofibrils were entirely pushed to one side by lipid droplets creating an area which was entirely free of neurofibrils, but was extremely argentophillic—staining well with his silver stain.

Also although silver stains are also known to be very sensitive in the staining of bacteria, apparently unknown to Bielschowsky, silver nitrate also binds to the outer layers of the tubercle bacilli, allowing its visualization as well. By 1911, Von Getegh had described a method showing that silver nitrate brought tubercular spores into sharp relief. This was followed by the findings of Egon Darzins, who later worked at the Robert Koch Institute in Berlin, when he recognized that the tubercular bacilli could be stained with silver nitrate [51].

Another clue to the “chemical conversion of the neurofibrils” that Alzheimer stipulated surfaced in 2004, approximately one hundred years after Alzheimer’s presentation in Tübingen. German scientists, working mere blocks away from where Alzheimer gave his talk, established that the renegade protein called “tau” constituting at least in part the chemical conversion that Alzheimer was trying to describe could be generated in the brains of laboratory animals inoculated with tubercular elements [52]. If normal tau protein nourished a neuron’s axon, the abnormal “hyperphosphorylated” tau after mycobacterial attack formed sticky clumps, much like what happened with Alzheimer’s beta-amyloid plaque, resulting in the death of the neuron. Tuberculosis itself contains a phosphatide fraction with 3 percent phosphorus and has the ability to phosphorylate CNS tissues, including neurons [53]. Not only can TB produce the same protein phosphorylation [54,55] seen in autopsied Alzheimer’s brains, [56] but the very same inflammatory neurotoxic proteinase and cytokines instrumental in the creation of beta-amyloid plaque, tau aggregation, and neurofibrillary tangles in Alzheimer’s [57]

are operative and found elevated also in the phosphorylated tissue specimens from patients with CNS tuberculosis [53].

As late as 1930, Lubarsch wrote the following:

“It is not emphasized enough that, as it seems, amyloid never affects the central nervous system; this fact has already come to the attention of Virchow. I, myself, in spite of particular circumspection, in cases of most intense generalized amyloidosis, have never found even traces of amyloid (in the brain)” [58].

How wrong this would prove to be.

Department of Neuropathology, Harvard Medical School, Boston, Massachusetts, 1909

By 1910 within three years of Alzheimer and Fischer’s initial papers, Elmer Ernest Southard, Harvard professor of neuropathology, released his own paper on senile and Alzheimer’s presenile dementia.

In that paper, Southard put Alzheimer and Fischer on notice that with regard to age-related senility, his autopsy of forty-two cases of what we now call Alzheimer’s disease showed that the vast majority of cases had findings suggestive of tuberculosis—as a rule dormant, obsolescent, and acquired earlier in life. Furthermore, Southard reported straightforwardly that general tuberculosis could “scarcely be excluded with safety from any case” in his experience autopsying the age-related dementias [59]. In addition, Southard, an expert on the pathology of neurosyphilis, found no one-on-one linkage between neurosyphilis in either Alzheimer’s or senile dementia [60] (**Figure 9**).

Kraepelin and Alzheimer’s response to Southard’s work was to ignore it. But Southard, regarded as the leading neuropathologist in the United States, was difficult to ignore, even for Germany’s most ardent psychogenicist and psychiatric classifier-in-chief, Emil Kraepelin.

This was not the first time that Southard and Kraepelin had crossed swords. And Kraepelin would soon have more than enough of Southard, who was a major force behind the eventually successful attempt to change Kraepelin’s pet popularization of “dementia praecox” back to schizophrenia (**Figure 10**) [61].

Southard was quite blunt and to the point, regarding Kraepelin’s championing of the term “dementia praecox.” It meant “premature dementia,” a chronic yet rapid deterioration of thought ability that usually begins in the late teens or early adulthood. Though aware that Arnold Pick first used the term in 1891, Southard was nevertheless irked by Kraepelin’s continued attempts to disseminate it. He complained accordingly:

“Perhaps no more unfortunate term than dementia praecox has yet been devised for an important group of psychopathic patients” [62].



Figure 9 Dr. E. E. Southard, MD, Director of Harvard Neuropathology.

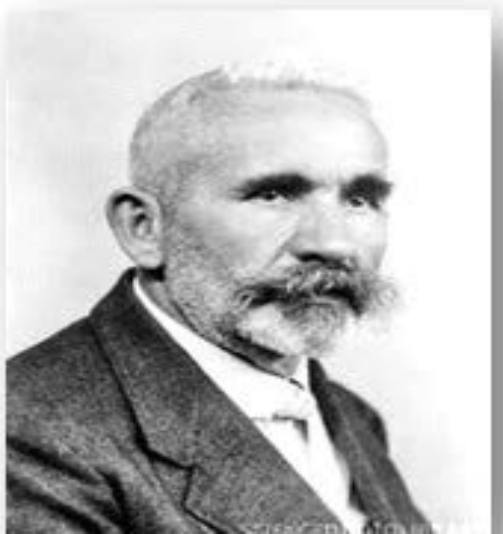


Figure 10 Emil Kraepelin.

Although E. E. Southard subsequently would become Chairman of the Committee on Psychiatry and Neurology for the National Research Council, his research focused squarely on neuropathological studies—totally uninfluenced by psychiatry. Unlike Alzheimer, Southard had no Kraepelin to pay homage to. Kraepelin was after a brand-new illness, preferably unknown regarding cause for the sake of the financial perpetuation of his clinic. Kraepelin knew Southard's tubercular/dementia reference well, made more than familiar to him through the publications of still another one of Kraepelin's rivals, England's T. S. Clouston. In his memoirs, Kraepelin mentions Clouston's visit to Munich:

"Englishmen rarely came to visit, amongst the more well-known colleagues, Clouston came to visit" [63].

Office of the Director, Royal Edinburgh Asylum, Edinburgh, Scotland, the UK, 1911

Clouston was "well-known," indeed. In fact, his fame at that time easily rivaled Kraepelin's. Of the two benchmark events chronicled to this day in medicine for 1883, Thomas Clouston's publication of *Clinical Lectures on Mental Diseases* sits side-by-side with Emil Kraepelin's *Compendium der Psychiatrie*.

Clouston was appointed Lecturer on Mental Diseases at the prestigious University of Edinburgh, a post he held in conjunction with his position as head of the noteworthy Royal Edinburgh Asylum (**Figure 11**). A celebrated lecturer, Clouston gained international notoriety for his explanation of the psychiatric disorders of adolescence. Publishing extensively, Clouston began with his remarkable *Clinical Lectures*, followed, later, by his more popular *Unsoundness of Mind* [64].

But in far-off Scotland, where he read about Aguste Deter, Sir Thomas Clouston could not in any way agree with Alzheimer's thoughts or conclusions. To Clouston, Deter represented neither a "new disease" nor what Alzheimer referred to as "a peculiar, little-known disease process." Clouston, a contemporary of Alzheimer, would die in 1915 eight months to the day before Alzheimer's death. Clouston wasn't just a psychiatrist; at the time he was superintendent of the prestigious Royal Edinburgh Asylum and previous to that, president of the Royal College of Physicians. Both Alzheimer and Clouston would soon hold international reputations, each considered a pioneer in the treatment of mental illness. Yet for the life of him, Sir Thomas Smith Clouston thought the case of gaunt, suspicious, hallucinatory, paranoid-like Auguste Deter an open and shut case of what he often referred to in his lectures at Edinburgh University as "monomania of suspicion." Clouston said this:

"This is a good example of those cases of pure monomania of suspicion, almost all of whom, according to my statistics, die of tuberculosis" [65].



Figure 11 Sir Thomas Smith Clouston.

As for the more demented cases such as Deter's, with her incapacitating memory loss, Clouston added this statement:

"This happens in about 30% of cases. It is the event we most dread. It is the equivalent to a mental death" [66].

So common was the knowledge at Alzheimer's time that tuberculosis (TB), in any form, whether inside or outside of the central nervous system, could lead to memory loss—some of it severe and progressive—that Clouston was just amazed at the exquisite lengths and efforts that Alzheimer and his boss, Kraepelin, went to totally ignore it. The fact that central nervous system tuberculosis could masquerade as an age-related Alzheimer's dementia with severe memory loss was and still is documented to this day [67].

Clouston maintained that since tuberculosis's psychiatric symptoms and dementia appeared long before the disease itself advanced to any great degree, many patients committed with TB were being sent to asylums instead of special hospitals for the treatment of the disease. Carpenter, in a 1903 review in *The Journal of the American Medical Association*, found Clouston's opinions not only justified but "a decisive etiologic (causative) factor" in any discussion of a subset of all asylum populations, including the one Auguste Deter now found herself in [68]. Forbes Winslow of Sussex House Hammersmith, himself a former president of the Royal College of Psychiatry prior to Clouston, had documented what neurotuberculosis could do to the mind in a clear and methodical way. Winslow presented cases of severe mental loss at the hands of neurotuberculosis [69]. Among them, a gentleman, aged fifty-four who worked as a principal in a fairly large school and who died of "softening of the brain," as his tubercular disease choked off vital blood supply to that portion of the brain. This man, who was Deter's age, had admitted at the time to his medical attendant that his mind was "gradually fading away from him," yet he carried on, occupying himself with his usual workday duties until one day he could not. Winslow said this: *"Immediately retiring to his own private room, he seated himself in a chair, burst into a flood of tears, exclaiming, in wild despair, 'My mind is gone! Altogether gone!'"* Ibid., p. 327.

Clouston thought it odd, then, that in 1905, a year before Deter died, Paul Claisse and his colleague, Dr. Abrami, presented a case to the Medical Society of the Hospitals of Paris, with much the same symptomatology of Frau Deter, both psychiatrically and neurologically [70]. But in this case, a spinal tap was offered and performed, something which Deter's family was never afforded the opportunity of choosing. The spinal fluid drawn from this patient showed lymphocytosis (an increase in those white blood cells called lymphocytes). And when it was injected into a guinea pig, that guinea pig abruptly expired—of tuberculosis.

Clouston, in a 463-subject autopsy-driven-study, said that tubercular patients tended to be demented before death much more than the non-tubercular. Furthermore, in the majority of cases of dementia, whether presenile or senile, Clouston found tuberculosis upon autopsy after death provided it was looked for adequately. The only problem was, according to Clouston, that nobody, including Kraepelin and Alzheimer and with the

exception of Southard at Harvard was adequately doing so.

Actually, Thomas Clouston was proving to also be an annoying thorn in Emil Kraepelin's side—on several levels. Clouston first coined the term "adolescent insanity" in 1873 for what Emil Kraepelin now insisted was dementia praecox. Clouston maintained that it was a serious condition from which 30 percent of victims wound up with a more serious "secondary dementia." This subset of Clouston's patients seemed in accord with Bleuler, who advanced the theory that Kraepelin's so-called "dementia praecox" of adolescence and certain senile dementias were identical.

Clouston knew all about the arbitrariness of Kraepelin's classifications, as well as Kraepelin's fondness for borrowing the terminology and concepts of others. Kraepelin had lifted his entire idea for a comprehensive psychiatric classification system directly from the writings of fellow German psychiatrist Karl Kahlbaum. So when Kraepelin used the term "dementia praecox" for what Clouston had already labeled "adolescent or developmental insanity" without specifically mentioning Clouston, Clouston felt angry, usurped, and slighted:

"Since I first used the term in 1873 and described its general characteristics, it has become generally accepted by writers in psychiatry. Lately, however, Kraepelin has taken the term dementia praecox and applied it to practically my whole group of adolescent cases, making it cover the curable and incurable. I strongly object..." [66].

Just as annoying, from Kraepelin's viewpoint, was Clouston's finding that most of the people who died of tuberculosis in mental institutions were demented and that Clouston's third stage of tubercular dementia in effect mirrored the symptoms of end-stage Alzheimer's, leading to "the abolition of mind in all its forms, of senile dementia" [64].

To Emil Kraepelin, this was a high-stakes conflict, and Kraepelin knew that very well. If there was a direct infectious continuum involving the evolution of dementia praecox/schizophrenia to Alzheimer's presenile dementia and then on to senile dementia itself, then two of Kraepelin's cherished categories praecox and Alzheimer's disease were in jeopardy. Indeed the term "Alzheimer's disease" would be superfluous a mere pit stop as dementia praecox evolved in some people toward senile dementia.

Anatomie Laboratorium, Nervenlinik, Department of Clinical Psychiatry, University of Munich, Germany, 1910

Showing all the assurance of a favored son, Alzheimer's young workhorse, Gaetano Perusini, proceeded to autopsy the four cases Alzheimer assigned to him, the first of which was the brain of Auguste Deter. Perusini was bright. Perusini was intuitive. In addition, Perusini spoke fluent German. But Perusini was also rather young and clinically unseasoned, having graduated from the School of Medicine of the Catholic University in Rome and then having specialized mainly in the "endemic cretinism"

prevalent in northern Italy — Tabes Dorsalis of syphilitic origin, and Friedreich's condition [71]. He would work in Alzheimer's laboratory until 1912 and die within three years of his departure, a young life cut short while trying to save a fellow soldier during World War 1 (Figure 12).

When Alzheimer published the fourth volume of his book emphasizing abnormal tissue in the cerebral cortex of brains with mental disease, one of its chapters was titled "*The Perusini Cases.*" Perusini helped Alzheimer define Alzheimer's disease so much that some, to this day, call it "la malattia di Alzheimer-Perusini" ...the disease of Alzheimer-Perusini [72].

One of the Alzheimer's autopsies Perusini performed was on a syphilitic. But that patient also had apical lung scarring from pulmonary tuberculosis. The other three patients assigned to him did not have syphilis. Perusini knew that with regard to syphilis being behind Alzheimer's disease that Alzheimer, as well as Oskar Fischer of Prague, never gave even a hint or implication that syphilis was exclusively or largely behind Alzheimer's. Perusini indicated that in syphilis, "the brain usually lacks the described plaques and ganglion cell alterations" yet it was in this case of syphilis along with lung scarring from a previous tubercular attack that Perusini saw just such plaques and tangles. Perusini called the tubercular lung lesion "old" yet simultaneously left the door open in general to an "old" cause for his Alzheimer's patients. He noted that:

"All observations in the cerebral cortex (including plaques and tangles) and particularly in the glia indicate with certainty that we are dealing with an old pathological process that advances over the course of years" [50].

Simchowicz was first to use the term "senile plaque." The term "plaque," however, has not historically been reserved for either Alzheimer's disease or senile dementia. As far back as 1830, Papavoine [73] described the tubercles of tuberculosis as "plaques" and granulations in the brain's pia mater, the very area that Perusini now saw major Alzheimer's alterations in (Figures 13).



Figure 12 Gaetano Perusini, 1910.

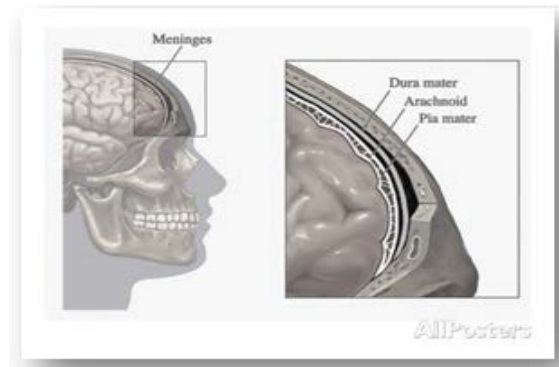


Figure 13 The pia mater, or "pia," which is the innermost of the three coverings of the brain called the "meninges." The pia mater, as shown above, firmly adheres to the surface of the brain and spinal cord. It is a very thin membrane but highly vascular and filled with small blood vessels.

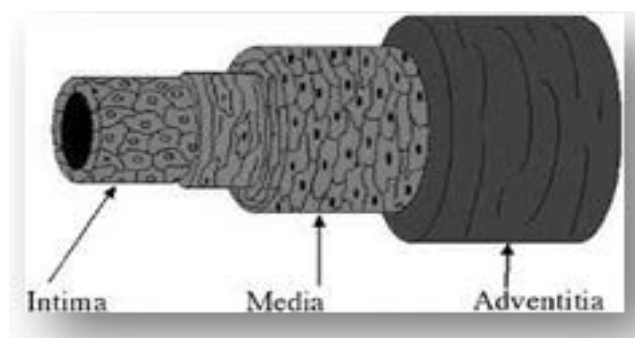


Figure 14 The layers of an artery. Its adventitia is on the outside, the external coating of a blood vessel. The adventia is a tough layer consisting mainly of collagen fibers that act supportively. Perusini found thickening of the Alzheimer's adventia.

Papavoine was not the first to study the pia with regard to tuberculosis. Previously, Rindfleisch closely followed the histology of miliary tubercles in the pia, finding the larger arteries to be the seat of unilateral swelling, while the smaller arteries presented spindle-shaped thickenings all originating in the adventitia of blood vessels [74]. **Figure 14.** Fischer described similar spindle-shaped thickenings of nerve fibers terminating with club forms in plaques.

To Barlow, such infiltration of the pia with cerebral tuberculosis could also lead to the classic Alzheimer's degeneration reported by Fischer and Alzheimer of both the central mass of nerve fibers (axis-cylinders) and ganglion cells leading, at times, to neurofibrillary tangles [16]. By 1915, Sir William Osler spoke of the "plaque" of focal tuberculous meningoencephalitis, usually situated on the surface of one of the cerebral hemispheres and less often elsewhere [75]. Although of meningeal origin, Osler said, the involvement of cortical tissue from such tubercular plaque was inevitable.

Gaetano Perusini continued to summarize his Alzheimer's findings:

"A further common finding in all three cases (that were not syphilitic) concerning the blood vessels is the thickened appearance of the adventitia, earlier described. This adventitial enlargement was common to both small and large blood vessels of the brain: at times, presented as quite strange thickenings, occasionally only involving one side of the blood vessel. At times this gave a half moon appearance in the Van Gieson preparation while in others, the blood vessel sometimes appears as a thick lumen-less (closed) red ring so that it could be confused with amyloid bodies..." [50].

Approximately two and a half decades before this, Guarneri studied the histological changes in twelve cases of tuberculous meningitis, seeing similar thickened adventitia, with the same strange semilunar half-moon thickenings that Perusini mentions, occasionally involving one side of the blood vessel [76]. And fourteen years before Perusini, Hektoen, in the *Rockefeller Journal of Experimental Pathology*, saw similar vascular changes in cerebral tuberculosis "in the form of a homogeneous ring which stains...bright red with Van Gieson's stain" and with particular thickening, once again, of the adventitia [77].

So according to Hektoen, Perusini's findings of thickening of the Alzheimer's adventia simulate what happens when tubercle bacilli, carried by the blood, are localized in the arterial adventitia. In fact, "In cerebral arteries only the adventitia is usually involved," Hektoen wrote. He added, "All authors emphasize the prominent part played by the adventitia in the formation of the tubercles and more diffuse infiltrations in tuberculous meningitis [77]. This, Hektoen said, was because it was in the lymph spaces in this adventitial layer of the arterial wall that the tubercle bacilli appeared to find the most favorable conditions for rapid growth.

Perusini's summary of tissue changes generally found in Alzheimer's continued to mirror Hektoen's findings on tubercular changes involving the brain. When Perusini talked about the ability of Alzheimer's to make changes in the intima of pial arteries as well as the arterial adventitia, Hektoen made this statement:

"The general conclusion is consequently warranted that in tuberculous meningitis of bloodborne infection an unexpectedly frequent and significant localization of the bacilli occurs upon the intima of pial arteries in addition to that in the arterial adventitia" [77].

Perusini also noted that plaque and tangle formation in all four of his cases of Alzheimer's were limited to the cerebral cortex, even in the one case with severe spinal-cord involvement. Hektoen observed that tuberculosis, with time, also preferred to attack the cerebral cortex.

Just months earlier, Perusini saw Kraepelin shaken when the American professor, Southard, now at Harvard, published autopsy-based linkage of active or dormant TB to Alzheimer's. By all indications, E. E. Southard was one of the most remarkable physicians in early twentieth-century medicine. In fact, Southard had reported that general systemic tuberculosis could "scarcely be excluded with safety from any case" of age-related dementia or Alzheimer's disease [59].

The single worst disease present in European cities was tuberculosis, and even by 1800, it was understood that no other disease was as common or as deadly. Yet Perusini knew that Alzheimer and Kraepelin both paid little attention to the one disease except for syphilis that could possibly account for the sudden rise in age-related dementias.

Office of Medical Research Director, the State Institute for Geriatrics, Warren, Pennsylvania, 1972

As he read Oskar Fischer's turn-of-the-century study in the 1970s, nothing, including Fischer's referencing a tubercle, and the "miliary" tubercular-like distribution of Alzheimer's brain plaque, seemed out of order to Pennsylvania neuropathologist Philipp Schwartz (**Figure 15**). Nor could he find any fault in Southard's Alzheimer's autopsy conclusions at Harvard or Clouston's original research implying Alzheimer and the senile dementias as being a result of old and mostly dormant foci of TB. Rather, Schwartz's findings were comparable. Schwartz made this observation:

"Chronic infections, and particularly tuberculosis, have heretofore been regarded as the most frequent and therefore the most important cause of systemic amyloid degeneration. This fact induced us to look for sequels of pulmonary tuberculosis in around 150 cases of senile and presenile (Alzheimer's) amyloidosis. Postmortem roentgen photography, as well as careful macroscopic and histologic examination of the lungs, disclosed typical calcifications of healed intra-pulmonary or lymphoglandular tuberculous infiltrates in almost every instance of this series, and quite often typical cicatrices of old lymphonodular bronchial lesions. Doubtless, the great majority of our senile and presenile patients displaying cerebral amyloidosis, suffered from pulmonary tuberculosis sometimes before symptoms of senile deterioration arose" [78].

Originally a Swiss pathologist, Schwartz, a student of Loeffler, having completed his work in Ankara, moved to the United States to become Director of Research at the Pennsylvania



Figure 15 Professor Dr. Med. Philipp Schwartz American Medical Association Award USA, 1960.

State Institute in Warren. There, through extensive human and animal autopsy-driven studies, Schwartz almost invariably found tubercular foci in Alzheimer's bodies usually latent. Though seemingly dormant, he knew that such foci could reactivate at any time, leading through either immunologic mechanisms or direct systemic invasion to tissue changes identical to those seen by Fischer and Alzheimer [78,79]. It is unclear why the elites of American medicine shelved Schwartz's extensive and well-documented neuropathological work on Alzheimer's, other than the fact that it brought up a topic both out of their comfort zone and interest—a wider role for cerebral tuberculosis.

One of the main reasons why Dr. Philip Schwartz could go where few had gone before him was his introduction of a critical method, still used today, whereby the flouochrome dye Thioflavin-S lit up amyloid deposits, both in humans and animals. Using this process, Schwartz proceeded to fashion the textbook *Amyloidosis: Cause and Manifestation of Senile Deterioration* which stands as a monument to the course that solid basic research on Alzheimer's and the amyloid neurodegenerative disorders could have taken.

Neurosyphilis had diminished to a point of rarity, and Schwartz saw amyloidosis both "primary" (supposedly noninfectious) and secondary (infectious) in the brain and elsewhere, mostly as the by-product of underlying infectious tuberculosis, usually dormant. Such infection could then, with time or age, either reactivate itself or be reactivated by a host of traumatic, chemical, biologic, or physical insults. He had autopsied hundreds of cases. In each case, animal or human, he documented plaque in the brain, accompanied by the amyloid degeneration of nerve fibrils as a result of systemic infection.

Schwartz injected *M. tuberculosis* into the peritoneal sac of twenty-two guinea pigs, all of whom died within twenty-eight to ninety-six days [79]. All but four exhibited amyloidosis. Yet only one of his control animals came down with amyloidosis. With his guinea pig experiment, Schwartz supported the findings of Hass, who in a large series of rabbits found that three out of every four animals developed amyloidosis within fifteen days of being infected with bovine tuberculosis. Furthermore, the injection of tuberculin into Haas's animals only hastened the development of amyloidosis [80].

In his multipart amyloid study for the Archives of Pathology, Hass and his colleagues made this conclusion:

"In the present investigation, the only infectious disease which served as an apparent cause of amyloidosis was tuberculosis" (80 p. 228).

All twenty-one of Hass's human subjects with amyloid disease had chronic pulmonary tuberculosis due to the human tubercle bacillus.

Conclusion

Throughout Alois Alzheimer's papers, it is both remarkable and frankly inexplicable that despite the available, huge amount of peer studies done on tubercular attack on the brain and the nervous system degenerative or otherwise—Alzheimer never

considered this disease in any of the differential diagnoses found in his many publications. Thus, although Neurologist/psychiatrist/pathologist Alois Alzheimer was technically excellent in his neuropathological presentations, his laboratory preparations, and their assessment, he seemed lacking in his differential diagnosis. But, then again, even scientific icons can be mistaken.

By late 1912, Alzheimer, who had been appointed as the Chair of Psychiatry at the University of Breslau, took on the case of a twenty-seven-year-old woman of slow speech and weakness who experienced frequent vomiting [81]. Soon afterward, this patient experienced a noticeable stiffness in her gait, with accompanying weakness and sharp, intermittent, spasmodic pains in her left arm, which had increased in intensity. Alzheimer noted that she was depressed, often crying, which, in turn, sometimes resulted in convulsions. She was first sent to a tuberculosis sanatorium and then released to Dr. Ludwig Mann's private office. From there, and for questionable reasons, she found her way into a psychiatric clinic for a consult with Dr. Alzheimer, although Alzheimer admitted that she seemed completely rational and oriented when she was seen. In December 1911, her father died, and she was understandably shocked by the event. Yet Alzheimer made no attempt to chart the cause of her father's death.

So we have a young person, seriously physically sick, sent for a psychiatric evaluation. This in itself could go a long way in explaining her depression and crying. She was seeking a cure for a physical illness, and that cure seemed unreachable. After treatment in the TB sanatorium, she mentioned that there was temporary improvement, but it did not last long; her disease returned with a vengeance. Alzheimer also charted that when she swallowed, it was often the wrong way, and apparently food got "up her nose," a sign that Alzheimer realized showed possible bulbar involvement. But there was also the possibility of spinal involvement, causing what Alzheimer noted as "painful spastic convulsive states of extremities." The term "bulbar" means of or relating to a bulb, specifically involving the medulla oblongata, often called simply the medulla. The spine sits just below the medulla.

As for this patient's frequent vomiting, the medulla houses the chemoreceptor trigger zone (CTZ), which communicates with other structures in the vomiting center to initiate vomiting. The word "bulbar" can also refer to the nerves and tracts connected to the medulla, important in proper swallowing.

Alzheimer's write-up of this patient, posthumously edited and published by Spielmeier, was titled with reference to the symptoms: *"On a Peculiar Disease of the Central Nervous System with Bulbar Symptoms and Painful Spastic Cramps of the Extremities."* It appeared in *Zeitschrift fur die Gesamte Neurologie und Psychiatrie*. The word "peculiar" in this title is reminiscent of its similar use by Alzheimer for Deter's Alzheimer's disease:

"All in all we have to face a peculiar disease process. Such peculiar disease processes have been verified recently in considerable numbers" [82].

But how "peculiar" was either case?

This twenty-seven-year old governess was originally admitted to a TB sanatorium. Alzheimer knew his patient was running symptoms of bulbar palsy, which can include progressive difficulty with chewing, talking, and swallowing. Yet eight years before Alzheimer saw this patient, in 1905, Dr. D. J. McCarthy of Phipps Institute at Johns Hopkins described a similar case of bulbar palsy from cerebral tuberculosis, also with difficulty of swallowing, the same brief remission, the same weakness of the arms and legs, and the same fatal termination that Alzheimer's patient would soon experience. Accompanying this, mentioned McCarthy, "Not a cell in the spinal cord was in a normal healthy condition" [83]. It has long been known that severe tuberculous meningitis can, in certain cases, produce the same bulbar palsy that Alzheimer's patient had, either through blood-borne seeding or extension from the base of the brain downward to the medulla on its path to the spine [84].

The medulla is continuous with the spinal cord, which explains Alzheimer's patients' spinally related "painful spastic convulsive states of the extremities".

What is surprising is that this and other cases of CNS spinal involvement with or without TB meningitis were extraordinarily and widely documented in the literature both prior to and during Alzheimer's time. Kelynack, a UK neurologist, mentioned in 1908 just five years before Alzheimer saw his patient that when cerebral tuberculosis affects the spinal membranes, symptoms in the cervical region could include violent painful contractions in the arm, forearm, and shoulders, usually accompanied by weakness [85]. And lower down, in the lumbar spine region, inflammation from the disease could yield similar painful convulsions and weakness of the lower extremities, creating a stiffness of gait.

By all indications, this young woman was seriously sick and suffering from a systemic/neurological disease with general as well as neurologic symptoms. Yet when Alzheimer turned the case over for presentation to the Breslau Psychiatric-Neurologic Union in February of 1913, he weighed in with the awkward, if not reckless, conclusion that this young lady was suffering from a hysterical condition of the mind, as first popularized by Sigmund Freud. Alzheimer noted, "*An organic disease (such as neurotuberculosis) is unimaginable. Clinical observation points to a strong psychogenic (originating in the mind) suggestibility*" [47].

She simply was, then, according to Alzheimer, an open and shut case of psychiatric hysteria.

Dr. Ludwig Mann, extremely familiar with the case, did not agree. To Mann there was no question that the patient had chronic central nervous system disease, and he considered the hysterical symptoms a mere by-product of such disease. Mann could not have been more correct. Within four months of that presentation, this twenty-seven-year-old had seizures, ran a temperature of 41.8 degrees Celsius (107.24 Fahrenheit), became almost entirely unresponsive, and died. Obviously, then, this was a case of more than psychiatric hysteria, and it was time for some damage control. Alzheimer, after the girl's death, made this statement:

"Even if there could now be no doubt that an organic condition lay at the basis of the clinical picture (which there was no longer any doubt), it still appeared quite impossible to classify it with any known illness" [47].

Alzheimer's use of the term "impossible to classify it with any known illness" again sounds like his impression of Auguste Deter with her "Alzheimer's disease." Yet, at least in the case of the deceased twenty-seven-year-old, this statement proves to be presumptive. In the meantime, no serious effort, as with Deter, was exerted to perform a spinal tap or other diagnostics to rule out tubercular or other infectious disease.

Alzheimer then admitted what should have been his opening assessment to begin with:

"Our anatomic and physiological knowledge (of this case of the twenty-seven-year old) is burdened with countless gaps, which can for this reason easily lead us to erroneous conclusions" [47].

Such as jumping to the conclusion that this case was one of hysteria.

Yet when left with the grizzly task of autopsying this girl, Alzheimer's findings show serious pathology entirely unrelated to a mental condition. At one point, Alzheimer considered Wilson's disease (hepatolenticular degeneration) in his differential diagnosis. Wilson's disease is thought to be a genetic, copper- hoarding disease, but it should also be noted that acid-fast forms can cause chromosomal damage and genetic changes [86].

Although Alzheimer was unable to isolate any organisms during an autopsy from his patient, the stains he used and which microbes he was looking for were not clearly listed. Yet it was in Wilson's disease that Dr. Virginia Livingston and Dr. Eleanor Alexander-Jackson later would isolate acid-fast mycobacterial, tubercular-like microorganisms. Traditionally, since Koch (1882), mycobacteria such as tuberculosis and leprosy were identified by their capacity to retain certain red dyes such as carbol-fuchsin after being rinsed with acid alcohol, a common laboratory reagent. These microorganisms were and still are therefore called "acid-fast".

One of Livingston's cases of Wilson's disease involved a thirty-four-year-old woman. Livingston and Jackson found intracellular acid-fast microorganisms in mice and guinea pigs after injecting them with the bacteria isolated from this woman's blood. These animals then developed the same chronic disease of the liver, spleen, and brain that Livingston's patient had [87]. It is practically medical dictum that any Parkinson's patient under forty should be carefully checked for Wilson's disease [88]. A similar microorganism was cultured from the blood of meningoencephalitis patients by C. G. Burn at the Rockefeller Institute Hospital in New York [89]. But when, in 1970, Livingston and Jackson revisited Burns bacillus, they determined that it, too, stained "acid-fast" **Figure 16** [90].

Schömburg, like Breslau, is a town in Silesia, a spa town in the north of the Black Forest in Baden-Württemberg. Breslau sat only fifty-one miles west by southwest of where Alzheimer's Breslau clinic was. By 1911, Dr. Bruno Bandelier, medical director

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Figure 16 A small fraction of the literature directly pertinent to the signs and symptoms of the twenty-seven-year old governess's case—readily available to Dr. Alzheimer. Such citations regard tubercular involvement of the brain and spinal column. An exponentially greater number of references were in existence at that time.

of Schömberg's Schwarzwaldheim TB sanatorium, published A Clinical System of Tuberculosis Describing All Forms of the Disease [91]. The book, quickly picked up by William Wood and Company in New York, was also readily available to Alois Alzheimer in its original German version by 1911 a year and a half before he saw the ill-fated twenty-seven-year-old governess.

Bandelier wrote with physician Otto Roepke, at the time director of another German TB sanatorium at Stadwald in Melsungen, near Cassel. It is doubtful whether Alzheimer ever reviewed Bandelier and Roepke's *Die Klinik Der Tuberculose* or the hundreds and hundreds of well-documented references behind it, but by May 1912, obviously many in the German medical profession had. It required a second edition after only a year and a half and had become a virtual necessity for the medical profession. Its goal: to stimulate further interest in the clinical and practical recognition and treatment of the disease.

Bandelier and Roepke's English version was cited in the March 13, 1913, issue of *Nature* right along with Professors Alzheimer and Nissl's *Histological and Histopathological Work over the Cerebral Cortex* [92,93]. That Roepke and Bandelier would question Alzheimer's differential diagnosis in the case of the twenty-seven-year-old governess was a given. Besides the multitude of individual signs and symptoms Alzheimer listed that were compatible with tuberculosis of the nervous system, the authors had made this caution:

"Hysteria and tuberculosis approach each other closely. Even a slight tubercular infection, and still more fever, anemia, and inanition may in latent hysteria call forth such severe manifestations that the symptoms of tuberculosis may be masked by those of hysteria; such a condition has been called "hysterical tuberculosis" [92].

In no way could Otto Roepke agree with Alzheimer's diagnosis of the twenty-seven-year-old. Alzheimer's charting of "weakness" could quite conceivably have been from an anemia of a chronic disease such as tuberculosis, while inanition—lack of mental or spiritual vigor and enthusiasm—often comes across as depression. The symptom of "painful spastic convulsive states of the extremities" speaks for a spinal-cord involvement or compression from the disease, whereas the bulbar symptoms speak of involvement of the medulla.

Alzheimer died at only fifty-one, for reasons to this day not certain, but no one at any time has ever said that being a pathologist or neuropathologist was the safest of occupations. Historians report that Alzheimer's encounter with death began with a severe cold with flu-like symptoms, but that infectious endocarditis was responsible for his death.

As early as 1911, Bruno Bandelair and Otto Roepke published their book, in German, in which all of the postmortem explanations for Alzheimer's early death ("infectious angina," infectious endocarditis, nephritic kidney disease, and inflammatory disease of the joints) could be found to spring forth under the umbrella of blood-borne tuberculosis. So the question presents, could Alzheimer have been one of the seven million people worldwide whom TB killed each year at that time?

Infectious endocarditis is no stranger to systemic tuberculosis, as B. C. Millar points out [94]. But even before that, TB, a disease capable of infecting every organ in the body the heart no exception was first reported to cause a tubercular endocarditis (TBE) in 1892, and many other cases since [95]. British pathologist/researcher William Stark, explained how, after a flulike lung involvement, TB could and was carried by the bloodstream to various parts of the body, including the heart, the kidney, the joints, and the brain. It could then either turn into progressive disease or reactivate, even decades later. These were the "little lumps" that Stark uncovered on autopsy after autopsy. Pathologist Stark died at age thirty. Stark thus anticipated the tubercular findings of the famed Laennec, a contemporary of Parkinson. But after his death, Stark's words fell on deaf ears, only to become a curious controversy among students in various countries throughout Europe. Among these students was Bichat (1771–1882), a French pathologist who had autopsied countless tuberculous patients before he died of the disease at thirty-one, uttering as follows:

"Not much is really known about the pathology of phthisis (tuberculosis), for few autopsies have been done because of the foolish fear among physicians that the disease is catching" [96].

Both his own untimely death and the findings of Robert Koch would soon prove him wrong.

Just before Bichat died, seasoned pathologist Gaspard Laurent Bayle, also from France, predicted that tuberculosis was an infectious disease before this was proven. He was also first to describe the millet-like seed bodies as "tubercles." Bayle himself died at the age of forty-two. But it was Bayle's junior collaborator, René Laënnec, whom Parkinson personally knew, who would indelibly stamp on the Western mind that not only was tuberculosis infectious, but that it could literally attack every

tissue of the human body. Laënnec did hundreds of postmortem examinations of persons who had died of tuberculosis; he died at the age of forty-five.

Not all that much time had elapsed since Alzheimer's discovery of Alzheimer's disease when Neurologist I. J. Sands gave his talk on senile and presenile psychoses for a 1918 clinical conference at Columbia's Department of Neurology in New York City [97].

After a review of the age-related dementia literature, including that of Alzheimer and Fischer, Sands got around to his own work. Using Alzheimer's own descriptions of the tangles, plaque, and clinical progressive memory loss for a man in his forties, Sands matched Alzheimer with a case that he mentions typified Alzheimer's cases.

Sands first saw this patient, E. K., in late September 1917, and this patient died about a month afterward, three months after admission. Autopsy showed many of the changes typifying Alzheimer's age-related dementia, including a brain very much smaller than normal, definite temporal lobe atrophy, dilated ventricles, and an atrophic cortex. Microscopic findings included a somewhat thickened pia and a definite loss of cells in the first three layers of the cortex. There also was an increase in neuroglia, the presence of senile plaque, and whorls and the snarls of classic tangles.

But there was more. Just across from the bronchopneumonia, on the top of the right lung sat an area of tubercular involvement. And although Sands, relying on gross findings at autopsy, never did the exhaustive, painstaking slices and stains needed to rule out tubercular central-nervous-system involvement, he nevertheless realized that the disease had spread from the lungs through the blood to other organs because this patient's liver and spleen were also riddled with miliary TB. A gross autopsy nevertheless showed marked atrophy of the cerebrum, the beginning of plaque formation, and neurofibrillary changes. So Sands completed his summary of findings as marked cerebral atrophy, with plaques and tangles of the Alzheimer's type alongside chronic pulmonary tuberculosis of the lungs, liver, and spleen—a scenario not unlike what Southard, Schwartz, and Clouston repeatedly had reported.

By 2013 Mawanda and Wallace's "Can Infections Cause Alzheimer's Disease" struck down some of the commonly entertained pathogens for AD such as herpes simplex virus type 1, Chlamydia pneumoniae, and several types of spirochetes. Instead they pointed to two prime suspects for Alzheimer's amyloid-beta deposition: "especially chronic infections like tuberculosis and leprosy" [2].

Mawanda and Wallace's summation was correct, with the understanding that leprosy could not be behind Alzheimer's disease. This leaves us with but a single choice backed up by this historical review. And that choice is tuberculosis, its allied germs and moreover it's ever present and preferred cell-wall-deficient (CWD) configurations.

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